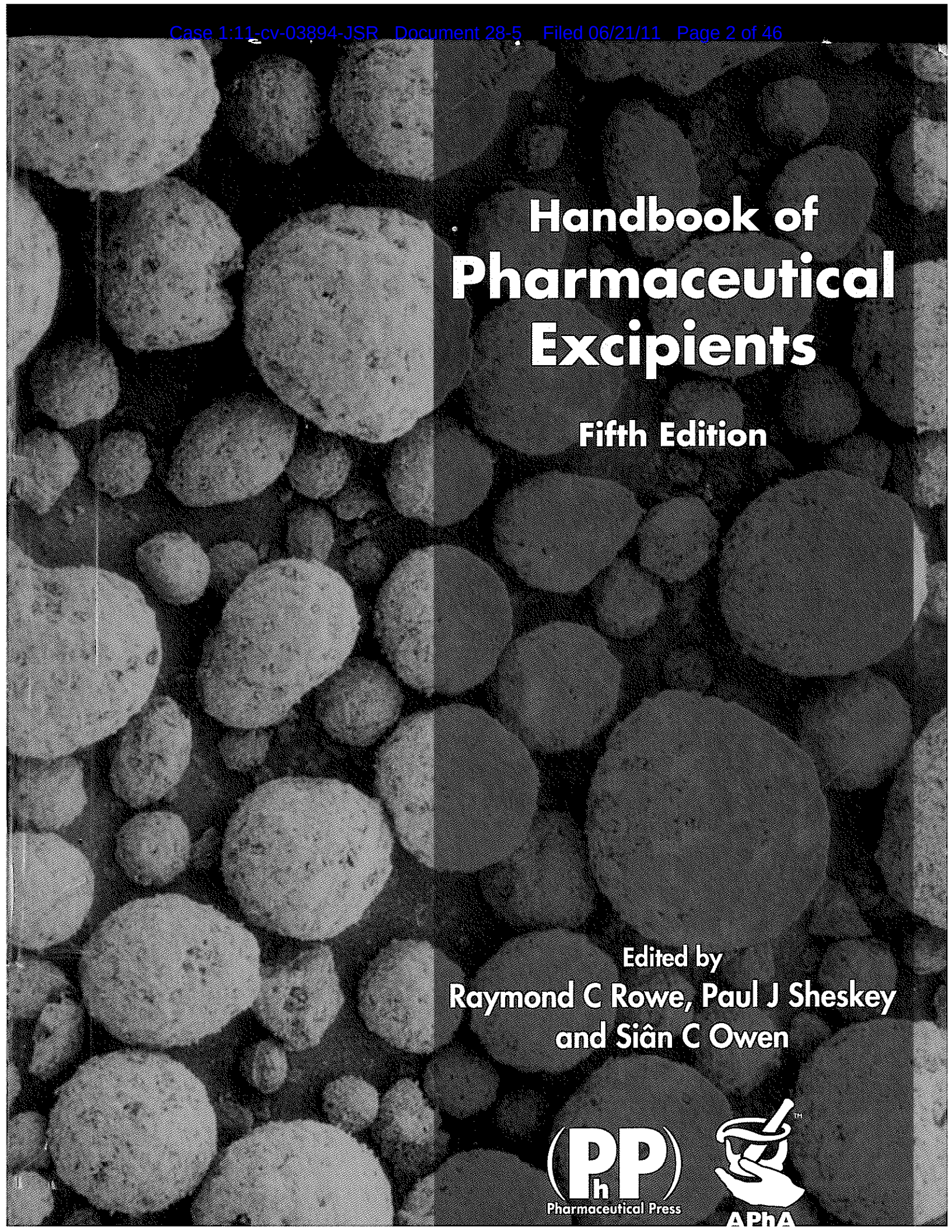
EXHIBIT 16



Handbook of Pharmaceutical Excipients

Fifth Edition

Edited by
Raymond C Rowe, Paul J Sheskey
and Siân C Owen

Pharmaceutical Press
APhA

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FIFTH EDITION

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Simethicone

1 Nonproprietary Names

BP: Simeticone
PhEur: Simeticonum
USP: Simethicone

2 Synonyms

Dow Corning Q7-2243 LVA; *Dow Corning Q7-2587*; polydimethylsiloxane–silicon dioxide mixture; *Sentry Simethicone*; simeticone.

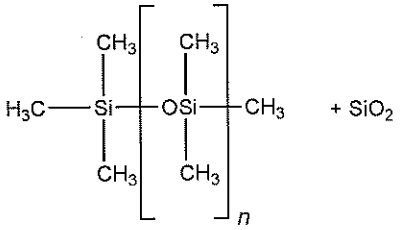
3 Chemical Name and CAS Registry Number

α-(Trimethysilyl-ω-methylpoly[oxy(dimethylsilylene)], mixture with silicon dioxide [8050-81-5]

4 Empirical Formula and Molecular Weight

See Section 8.

5 Structural Formula



where n = 200–350

6 Functional Category

Antifoaming agent; tablet diluent; water-repelling agent.

7 Applications in Pharmaceutical Formulation or Technology

The main use of simethicone as an excipient is as an antifoaming agent in pharmaceutical manufacturing processes, for which 1–50 ppm is used.

Therapeutically, simethicone is included in a number of oral pharmaceutical formulations as an antiflatulent, although its therapeutic benefit is questionable.[1] It is also included in antacid products such as tablets or capsules.[2–6] In some types of surgical or gastroscopic procedures where gas is used to inflate the body cavity, a defoaming preparation containing simethicone may be used in the area to control foaming of the fluids.

When simethicone is used in aqueous formulations, it should be emulsified to ensure compatibility with the aqueous system and components.

In the USA, up to 10 ppm of simethicone may be used in food products.

8 Description

The PhEur 2005 and USP 28 describe simethicone as a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$, stabilized with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiO-]$, and silicon dioxide. It contains not less than 90.5% and not more than 99.0% of the polydimethylsiloxane $[-(CH_3)_2SiO-]_n$, and not less than 4.0% and not more than 7.0% of silicon dioxide. The PhEur 2005 additionally states that the degree of polymerization is between 20–400.

Simethicone occurs as a translucent, gray-colored, viscous fluid. It has a molecular weight of 14 000–21 000.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for simethicone.

Test	PhEur 2005	USP 28
Identification	+	+
Characters	+	–
Acidity	+	–
Defoaming activity	≤15 seconds	≤15 seconds
Loss on heating	–	≤18%
Volatile matter	≤1.0%	–
Heavy metals	≤5 ppm	≤5 μg/g
Organic volatile impurities	–	+
Mineral oils	+	–
Phenylated compounds	+	–
Assay (dimethicone)	+	–
Assay (silicon dioxide)	–	4.0–7.0%
Assay (silica)	≤7.0%	–
Assay (polydimethylsiloxane)	90.5–99.0%	90.5–99.0%

10 Typical Properties

Boiling point: 35°C
Refractive index: n_D^{20} = 0.965–0.970
Solubility: practically insoluble in ethanol (95%) and water. The liquid phase is soluble in benzene, chloroform, and ether, but silicon dioxide remains as a residue in these solvents.
Specific gravity: 0.95–0.98 at 25°C
Viscosity (kinematic): 370 mm^2/s at 25°C for *Dow Corning Q7-2243 LVA*.

11 Stability and Storage Conditions

Simethicone is generally regarded as a stable material when stored in the original unopened container. A shelf-life of 18 months from the date of manufacture is typical. However, some simethicone products have a tendency for the silicon dioxide to settle slightly and containers of simethicone should therefore be shaken thoroughly to ensure uniformity of contents before sampling or use. Simethicone should be stored in a cool, dry, location away from oxidizing materials.

Simethicone can be sterilized by dry heating or autoclaving. With dry heating, a minimum of 4 hours at 160°C is required.

12 Incompatibilities

Simethicone as supplied is not generally compatible with aqueous systems and will float like an oil on a formulation unless it is first emulsified. It should not be used in formulations or processing conditions that are very acidic (below pH 3) or highly alkaline (above pH 10), since these conditions may have some tendency to break the polydimethylsiloxane polymer. Simethicone cannot normally be mixed with polar solvents of any kind because it is very minimally soluble. Simethicone is incompatible with oxidizing agents.

13 Method of Manufacture

Silicon dioxide is initially rendered hydrophobic in one of a variety of proprietary processes specific to a particular manufacturer. It is then slowly mixed with the silicone fluids in a formulation. After mixing, the simethicone is milled to ensure uniformity.

14 Safety

Simethicone is used in cosmetics, foods, and oral and topical pharmaceutical formulations and is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient. Direct contact with the eye may cause irritation.

Therapeutically, oral doses of 125–250 mg of simethicone, three or four times daily, have been given as an antiflatulent. Doses of 20–40 mg of simethicone have been given with feeds to relieve colic in infants.[7]

LD_{50} (dog, IV): 0.9 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Simethicone should be handled in areas with adequate ventilation.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (oral emulsions, powders, solutions, suspensions, tablets, and rectal and topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Cyclomethicone; dimethicone.

18 Comments

—

19 Specific References

1 Anonymous. Simethicone for gastrointestinal gas. *Med Lett Drugs Ther* 1996; 38: 57–58.
2 Sox T. Simethicone and sulfasalazine for treatment of ulcerative colitis. United States Patent 6,100,245; 1999.
3 Holtman G, Gschossmann J, Karaus M, *et al*. Randomized double-blind comparison of simethicone with cisapride in functional dyspepsia. *Aliment Pharmacol Ther* 1999; 13(11): 1459–1465.
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6 Devlin BT, Hoy MR. Semisolid composition containing an antiflatulent agent. European Patent 815864; 1998.
7 Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: randomized, placebo-controlled, multicenter trial. *Pediatrics* 1994; 84: 29–34.

20 General References

Daher L. Lubricants for use in tabletting. United States Patent 5,922,351; 1999.
Rider JA, Roorda AK, Rider DL. Further analysis of standards for antacid simethicone defoaming properties. *Curr Ther Res* 1997; 58(12): 955–963.

21 Authors

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22 Date of Revision

22 August 2005.

Sodium Lauryl Sulfate

1 Nonproprietary Names

BP: Sodium lauryl sulfate
JP: Sodium lauryl sulfate
PhEur: Natrii laurilsulfas
USPNF: Sodium lauryl sulfate

2 Synonyms

Dodecyl sodium sulfate; *Elfan 240*; sodium dodecyl sulfate; sodium laurilsulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; *Texapon K12P*.

3 Chemical Name and CAS Registry Number

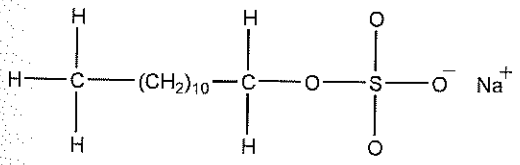
Sulfuric acid monododecyl ester sodium salt [151-21-3]

4 Empirical Formula and Molecular Weight

$C_{12}H_{25}NaO_4S$ 288.38

The USPNF 23 describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate ($C_{12}H_{25}NaO_4S$). The PhEur 2005 states that sodium lauryl sulfate should contain not less than 85% of sodium alkyl sulfates calculated as $C_{12}H_{25}NaO_4S$.

5 Structural Formula



6 Functional Category

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

7 Applications in Pharmaceutical Formulation or Technology

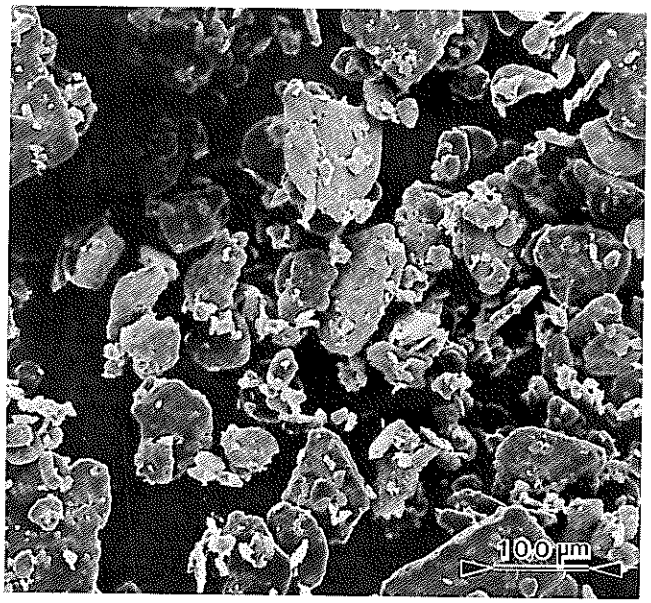
Sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics; *see* Table I.

It is a detergent and wetting agent effective in both alkaline and acidic conditions. In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins;[1] and sodium lauryl sulfate has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC).[2]

Table I: Uses of sodium lauryl sulfate.

Use	Concentration (%)
Anionic emulsifier, forms self-emulsifying bases with fatty alcohols	0.5–2.5
Detergent in medicated shampoos	≈10
Skin cleanser in topical applications	1
Solubilizer in concentrations greater than critical micelle concentration	>0.0025
Tablet lubricant	1.0–2.0
Wetting agent in dentrifices	1.0–2.0

SEM: 1
Excipient: Sodium lauryl sulfate
Manufacturer: Canadian Alcolac Ltd.
Magnification: 120×



8 Description

Sodium lauryl sulfate consists of white or cream to pale yellow-colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Acidity/alkalinity: pH = 7.0–9.5 (1% w/v aqueous solution)
Acid value: 0
Antimicrobial activity: sodium lauryl sulfate has some bacteriostatic action against Gram-positive bacteria but is

ineffective against many Gram-negative microorganisms. It potentiates the fungicidal activity of certain substances such as sulfanilamide and sulfathiazole.

Critical micelle concentration: 8.2 mmol/L (0.23 g/L) at 20°C

Density: 1.07 g/cm^3 at 20°C

HLB value: ≈40

Interfacial tension: 11.8 mN/m (11.8 dynes/cm) for a 0.05% w/v solution (unspecified nonaqueous liquid) at 30°C.

Melting point: 204–207°C (for pure substance)

Moisture content: ⩽5%; sodium lauryl sulfate is not hygroscopic.

Solubility: freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.

Spreading coefficient: −7.0 (0.05% w/v aqueous solution) at 30°C

Surface tension: 25.2 mN/m (25.2 dynes/cm) for a 0.05% w/v aqueous solution at 30°C

Wetting time (Draize test): 118 seconds (0.05% w/v aqueous solution) at 30°C

SEM: 2
Excipient: Sodium lauryl sulfate
Manufacturer: Canadian Alcolac Ltd.
Magnification: 600×

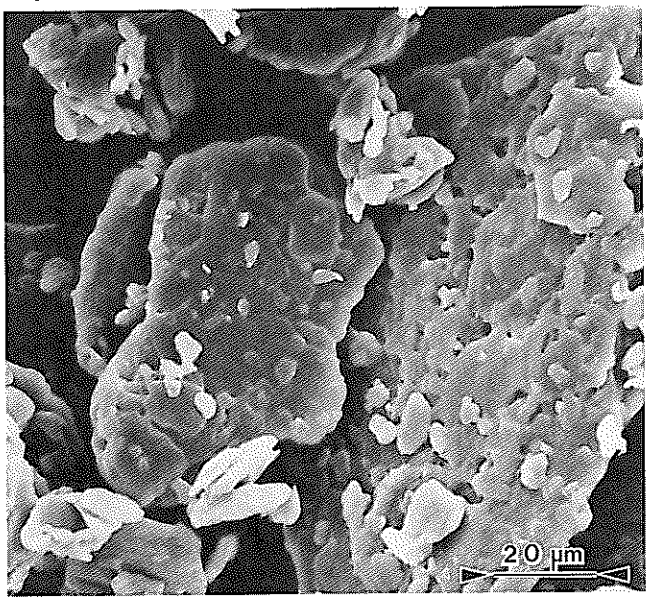


Table II: Pharmacopeial specifications for sodium lauryl sulfate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Alkalinity	+	+	+
Heavy metals	—	—	⩽0.002%
Sodium chloride	⩽8.0%	+	+
Sodium sulfate	+	+	+
Unsulfated alcohols	⩽4.0%	—	⩽4.0%
Nonesterified alcohols	—	⩽4.0%	—
Total alcohols	⩾59.0%	—	⩾59.0%
Organic volatile impurities	—	—	+
Water	⩽5.0%	—	—
Assay (as $C_{12}H_{25}NaO_4S$)	—	⩾85.0%	—

11 Stability and Storage Conditions

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e., pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate.

The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

12 Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions.

Solutions of sodium lauryl sulfate (pH 9.5–10.0) are mildly corrosive to mild steel, copper, brass, bronze, and aluminum. Sodium lauryl sulfate is also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

13 Method of Manufacture

Sodium lauryl sulfate is prepared by sulfation of lauryl alcohol, followed by neutralization with sodium carbonate.

14 Safety

Sodium lauryl sulfate is widely used in cosmetics and oral and topical pharmaceutical formulations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop.[3] Prolonged inhalation of sodium lauryl sulfate will damage the lungs. Pulmonary sensitization is possible, resulting in hyperactive airway dysfunction and pulmonary allergy. Animal studies have shown intravenous administration to cause marked toxic effects to the lung, kidney, and liver. Mutagenic testing in bacterial systems has proved negative.[4]

Adverse reactions to sodium lauryl sulfate in cosmetics and pharmaceutical formulations mainly concern reports of irritation to the skin[3,5–7] or eyes[8] following topical application.

Sodium lauryl sulfate should not be used in intravenous preparations for humans. The probable human lethal oral dose is 0.5–5.0 g/kg.

LD_{50} (mouse, IP): 0.25 g/kg[9]
LD_{50} (mouse, IV): 0.12 g/kg
LD_{50} (rat, oral): 1.29 g/kg
LD_{50} (rat, IP): 0.21 g/kg
LD_{50} (rat, IV): 0.12 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Inhalation and contact with the skin and eyes should be avoided; eye protection, gloves, and other protective clothing, depending on the circumstances, are recommended. Adequate ventilation should be provided or a dust respirator should be worn. Prolonged or repeated exposure should be avoided. Sodium lauryl sulfate emits toxic fumes on combustion.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (dental preparations; oral capsules, suspensions, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Cetostearyl alcohol; cetyl alcohol; magnesium lauryl sulfate; wax, anionic emulsifying.

Magnesium lauryl sulfate

Empirical formula: $C_{12}H_{26}O_4S{\cdot}HMg$
CAS number: [3097-08-3]
Comments: a soluble tablet lubricant.[10] The EINECS number for magnesium lauryl sulfate is 221-450-6.

18 Comments

A specification for sodium lauryl sulfate is contained in the Food Chemicals Codex (FCC). The EINECS number for sodium lauryl sulfate is 205-788-1.

19 Specific References

1 Smith BJ. SDS polyacrylamide gel electrophoresis of proteins. *Methods Mol Biol* 1994; **32**: 23–34.
2 Riekkola ML, Wiedmar SK, Valko IE, Siren H. Selectivity in capillary electrophoresis in the presence of micelles, chiral selectors and non-aqueous media. *J Chromatogr* 1997; **792A**: 13–35.
3 Wigger-Alberti W, Krebs A, Elsner P. Experimental irritant contact dermatitis due to cumulative epicutaneous exposure to sodium lauryl sulphate and toluene: single and concurrent application. *Br J Dermatol* 2000; **143**: 551–556.
4 Mortelmans K, Haworth S, Lawlor T, *et al*. Salmonella mutagenicity tests II: results from the testing of 270 chemicals. *Environ Mutagen* 1986; **8** (Suppl. 7): 1–119.
5 Blondeel A, Oleffe J, Achten G. Contact allergy in 330 dermatological patients. *Contact Dermatitis* 1978; **4**(5): 270–276.
6 Bruynzeel DP, van Ketel WG, Scheper RJ, von Blomberg-van der Flier BME. Delayed time course of irritation by sodium lauryl sulfate: observations on threshold reactions. *Contact Dermatitis* 1982; **8**(4): 236–239.
7 Eubanks SW, Patterson JW. Dermatitis from sodium lauryl sulfate in hydrocortisone cream. *Contact Dermatitis* 1984; **11**(4): 250–251.
8 Grant WM. *Toxicology of the Eye*, 2nd edn. Springfield, IL: Charles C Thomas, 1974: 964.
9 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004: 3258–3259.
10 Caldwell HC, Westlake WJ. Magnesium lauryl sulfate–soluble lubricant [letter]. *J Pharm Sci* 1972; **61**: 984–985.

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Hadgraft J, Ashton P. The effect of sodium lauryl sulfate on topical drug bioavailability. *J Pharm Pharmacol* 1985; **37** (Suppl.): 85P.
Nakagaki M, Yokoyama S. Acid-catalyzed hydrolysis of sodium dodecyl sulfate. *J Pharm Sci* 1985; **74**: 1047–1052.
Vold RD, Mittal KL. Determination of sodium dodecyl sulfate in the presence of lauryl alcohol. *Anal Chem* 1972; **44**(4): 849–850.
Wan LSC, Poon PKC. The interfacial activity of sodium lauryl sulfate in the presence of alcohols. *Can J Pharm Sci* 1970; **5**: 104–107.
Wang L-H, Chowhan ZT. Drug–excipient interactions resulting from powder mixing V: role of sodium lauryl sulfate. *Int J Pharm* 1990; **60**: 61–78.

21 Authors

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22 Date of Revision

15 August 2005.

Starch

1 Nonproprietary Names

BP: Maize starch
Potato starch
Rice starch
Tapioca starch
Wheat starch

JP: Corn starch
Potato starch
Rice starch
Wheat starch

PhEur: Maydis amylum (maize starch)
Solani amylum (potato starch)
Oryzae amylum (rice starch)
Tritici amylum (wheat starch)

USPNF: Corn starch
Potato starch
Tapioca
Wheat starch

Note that the USPNF 23 has individual monographs for corn (*Zea mays*), potato (*Solanum tuberosum*), tapioca (*Manihot utilissima* Pohl) and wheat starch (*Triticum aestivum*). The PhEur 2005 has monographs for each of these starches, except tapioca starch, along with an additional monograph for rice starch, *Oryza sativa*. Also note that the PhEur 2005 Suppl 5.0 contains an updated monograph for maize (corn) starch. The BP 2004 similarly describes maize, potato, rice, tapioca (cassava), and wheat starch in individual monographs, tapioca starch being obtained from the rhizomes of *Manihot utilissima* Pohl. The JP 2001 similarly describes corn (maize), rice, potato and wheat starch in separate monographs. *See also* Section 18.

2 Synonyms

Amido; amidon; amilo; amylum; *Aytex P*; *C*PharmGel*; *Fluftex W*; *Instant Pure-Cote*; *Melojel*; *Meritena*; *Paygel 55*; *Perfectamyl D6PH*; *Pure-Bind*; *Pure-Cote*; *Pure-Dent*; *Pure-Gel*; *Pure-Set*; *Purity 21*; *Purity 826*; *Tablet White*.

See also Sections 1 and 18.

3 Chemical Name and CAS Registry Number

Starch [9005-25-8]

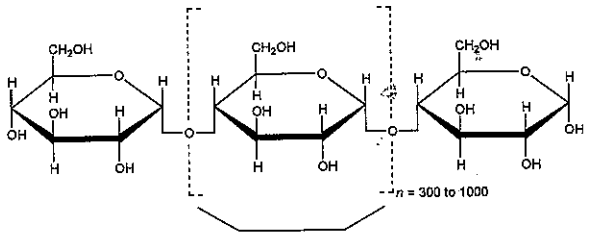
4 Empirical Formula and Molecular Weight

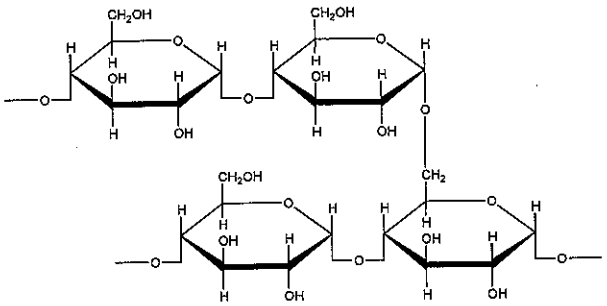
$(C_6H_{10}O_5)_n$ 50 000–160 000

where n = 300–1000.

Starch consists of amylose and amylopectin, two polysaccharides based on α-glucose. *See also* Sections 5 and 17.

5 Structural Formula





6 Functional Category

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.[1]

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w.[2–9] However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also, when used as a

disintegrant, starch exhibits type II isotherms and has a high specific surface for water sorption.[10]

Starch has been investigated as an excipient in novel drug delivery systems for nasal,[11,12] oral,[13–16] periodontal,[17] and other site-specific delivery systems.[18,19]

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Therapeutically, rice starch-based solutions have been used in the prevention and treatment of dehydration due to acute diarrheal diseases.

8 Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–6.5 for a 2% w/v aqueous dispersion of corn starch, at 25°C.

Compressibility: *see* Figure 1.

Density (bulk): 0.462 g/cm^3 for corn starch.

Density (tapped): 0.658 g/cm^3 for corn starch.

Density (true): 1.478 g/cm^3 for corn starch.

Flowability: 10.8–11.7 g/s for corn starch;[9] 30% for corn starch (Carr compressibility index).[20] Corn starch is cohesive and has poor flow characteristics.

Gelatinization temperature: 73°C for corn starch; 72°C for potato starch; 63°C for wheat starch.

Moisture content: all starches are hygroscopic and rapidly absorb atmospheric moisture.[21,22] Approximate equilibrium moisture content values at 50% relative humidity are 11% for corn starch; 18% for potato starch; 14% for rice starch; and 13% for wheat starch. Between 30% and 80% relative humidity, corn starch is the least hygroscopic starch and potato starch is the most hygroscopic. Commercially available grades of corn starch usually contain 10–14% water. *See also* Figures 2 and 3.

Particle size distribution:
Corn starch: 2–32 μm;
Potato starch: 10–100 μm;
Rice starch: 2–20 μm;
Tapioca starch: 5–35 μm;
Wheat starch: 2–45 μm.
Median diameter for corn starch is 17 μm and for wheat starch is 23 μm.

Solubility: practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37°C.[2,22] Polyvalent cations produce more swelling than monovalent ions, but pH has little effect.

Specific surface area:
0.41–0.43 m^2/g for corn starch;
0.12 m^2/g for potato starch;
0.27–0.31 m^2/g for wheat starch.

Swelling temperature:
65°C for corn starch;
64°C for potato starch;
55°C for wheat starch.

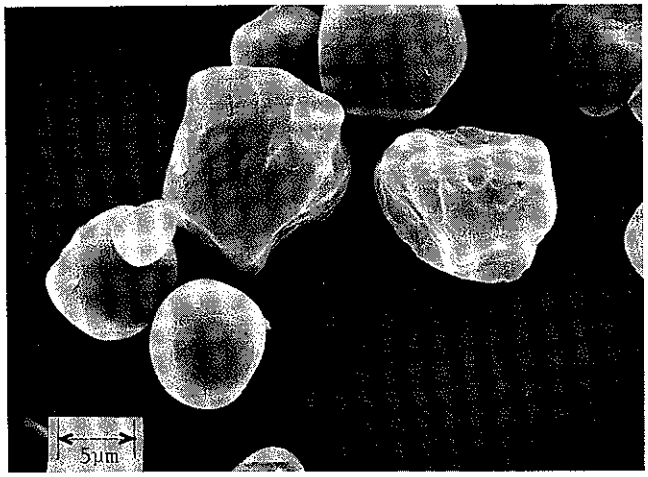
Viscosity (dynamic): 13.0 mPa s (13.0 cP) for a 2% w/v aqueous dispersion of corn starch at 25°C.

Table I: Pharmacopeial specifications for starch.

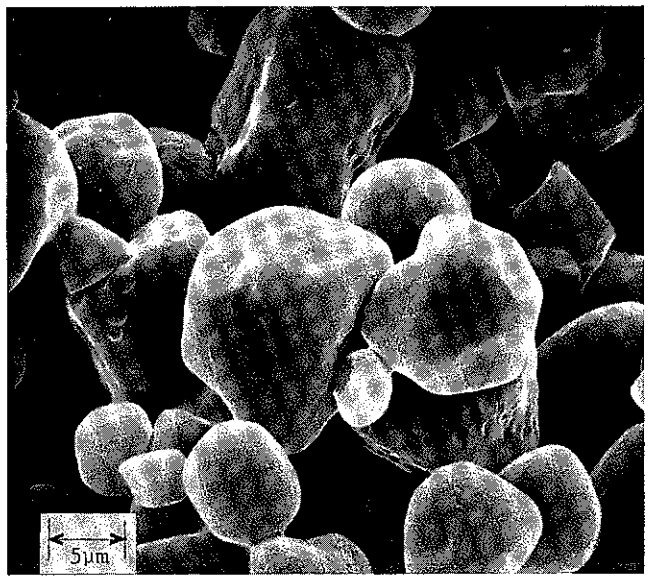
Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+[a]
Microbial limits	–	+	+
pH			
Corn starch	–	4.0–7.0[b]	4.0–7.0
Potato starch	–	5.0–8.0	5.0–8.0
Tapioca	–	–	4.5–7.0
Wheat starch	–	4.5–7.0	4.5–7.0
Acidity (rice starch)	–	+	–
Loss on drying			
Corn starch	≤15.0%	≤15.0%	≤15.0%
Rice starch	≤15.0%	≤15.0%	–
Potato starch	≤18.0%	≤20.0%	≤20.0%
Tapioca	–	–	≤16.0%
Wheat starch	≤15.0%	≤15.0%	≤15.0%
Residue on ignition	–	–	≤0.6%[a]
Sulfated ash			
Corn starch	≤0.5%	≤0.6%	–
Rice starch	≤1.0%	≤1.0%	–
Potato starch	≤0.5%	≤0.6%	–
Wheat starch	≤1.0%	≤0.6%	–
Iron			
Corn starch	–	≤10 ppm	≤10 ppm
Potato starch	–	≤10 ppm	≤10 ppm
Tapioca starch	–	–	≤0.002%
Wheat starch	–	≤10 ppm	≤10 ppm
Oxidizing substances			
Corn starch	–	≤20 ppm	≤20 ppm
Potato starch	–	≤20 ppm	≤20 ppm
Tapioca starch	–	–	≤0.002%
Wheat starch	–	≤20 ppm	≤20 ppm
Sulfur dioxide			
Corn starch	–	≤50 ppm	≤50 ppm
Potato starch	–	≤50 ppm	≤50 ppm
Tapioca	–	–	≤0.005%
Wheat starch	–	≤50 ppm	≤50 ppm
Total protein			
Corn starch	–	–	–
Rice starch	–	–	–
Potato starch	–	–	–
Wheat starch	–	≤0.3%	–
Foreign matter	–	+	–

[a] *See* USPNF 23 Suppl 1.0.
[b] *See* PhEur 2005 Suppl 5.0.

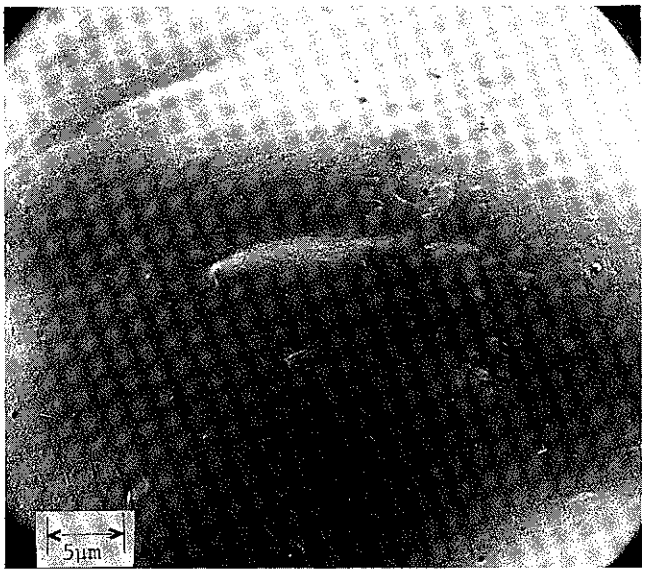
SEM: 1
Excipient: Corn starch
Manufacturer: Anheuser Busch
Lot No.: 96A-3 (67)
Magnification: 2400×
Voltage: 20 kV



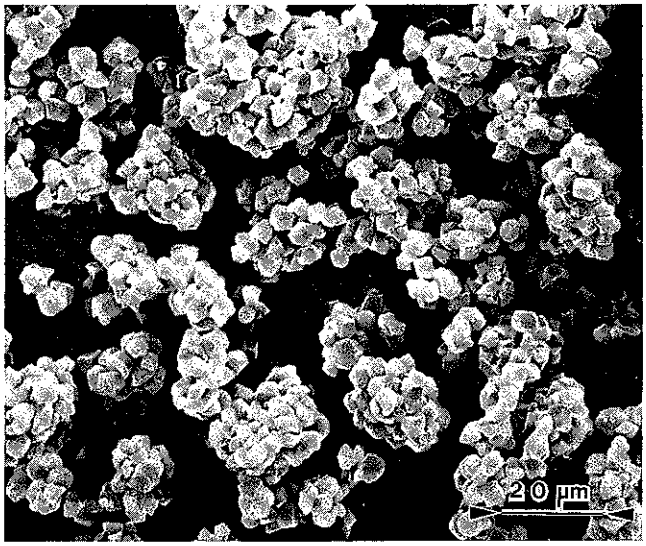
SEM: 2
Excipient: Corn starch
Manufacturer: AE Staley Mfg. Co.
Lot No.: 96A-4 (G77912)
Magnification: 2400×
Voltage: 20 kV



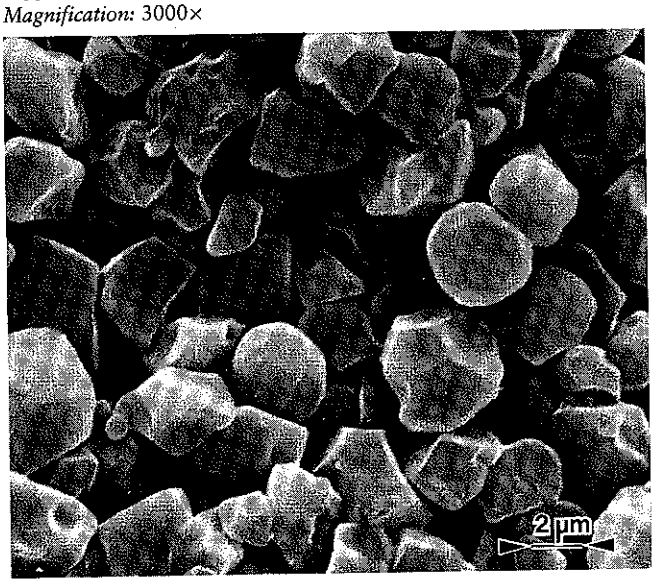
SEM: 3
Excipient: Potato starch
Manufacturer: Starchem
Lot No.: 96A-5 (1179)
Magnification: 2400×
Voltage: 20 kV



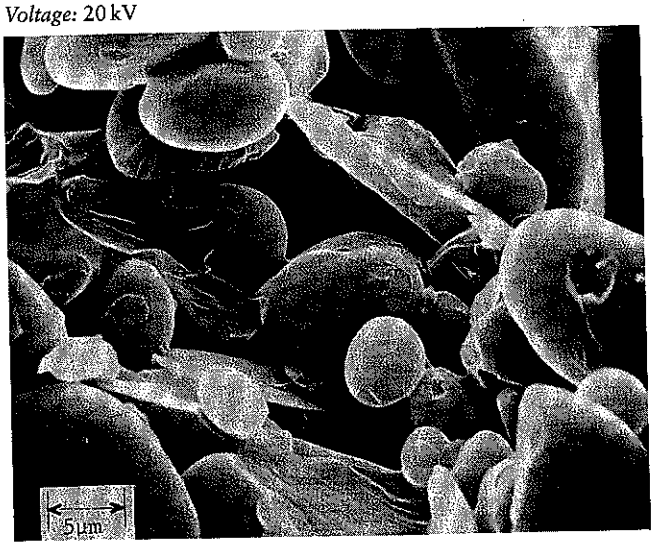
SEM: 4
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 600×



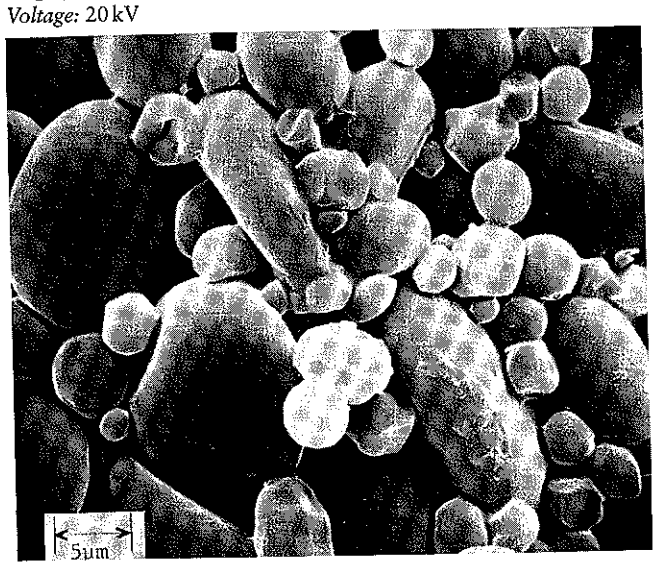
SEM: 5
Excipient: Rice starch
Supplier: Matheson, Coleman & Bell
Magnification: 3000×



SEM: 6
Excipient: Wheat starch (*Paygel 55*)
Manufacturer: Henkel Corp.
Lot No.: 96A-1 (2917D)
Magnification: 2400×
Voltage: 20 kV



SEM: 7
Excipient: Wheat starch (*Aytex P*)
Manufacturer: Henkel Corp.
Lot No.: 96A-2 (2919D)
Magnification: 2400×
Voltage: 20 kV



11 Stability and Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

Starch should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

—

13 Method of Manufacture

Starch is extracted from plant sources through a sequence of processing steps involving coarse milling, repeated water washing, wet sieving, and centrifugal separation. The wet starch obtained from these processes is dried and milled before use in pharmaceutical formulations.

14 Safety

Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets.

Starch is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material.[23] However, oral consumption of massive doses can be harmful owing the formation of starch calculi, which cause bowel obstruction.[24] Starch may also cause granulomatous reactions when applied to the peritoneum or the meninges. Contamination of surgical wounds with the starch glove powder used by surgeons has also resulted in the development of granulomatous lesions.[25]

Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source.

LD_{50} (mouse, IP): 6.6 g/kg[26]

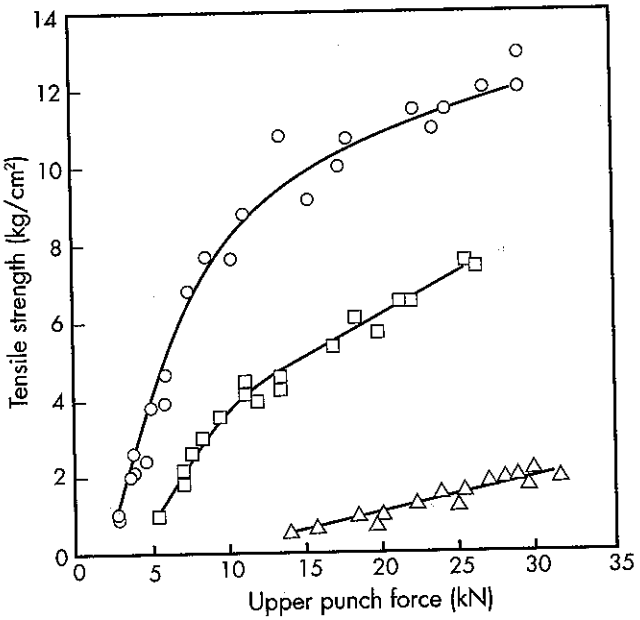


Figure 1: Compression characteristics of corn, potato and wheat starches.
□: Corn starch
○: Potato starch
△: Wheat starch
Tablet machine: Manesty F; speed: 50 per min; weight: 490–510 mg. Strength test: Diametral compression between flat-faced rams. Upper ram stationary, lower moving at 66 µm/s.

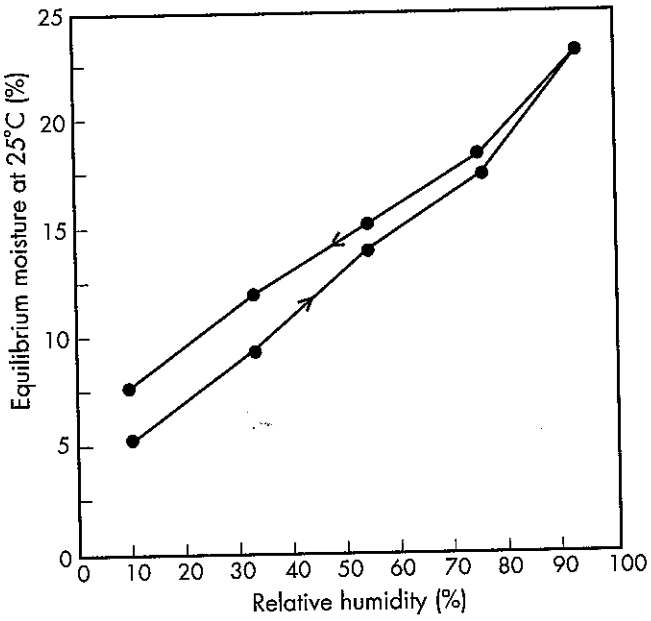


Figure 2: Sorption–desorption isotherm of corn starch. Anheuser Busch; Lot #67.

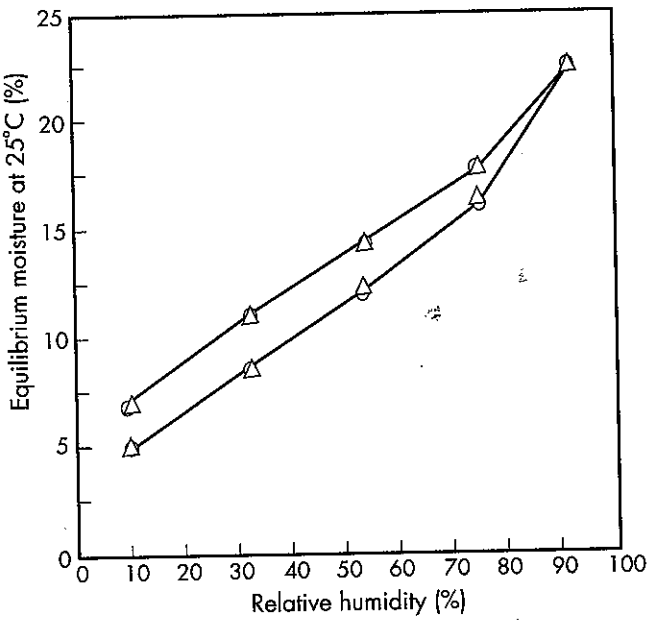


Figure 3: Sorption–desorption isotherm of wheat starch.
○: *Paygel 55* (Henkel Corp.; Lot #2917D)
△: *Aytex P* (Henkel Corp.; Lot #2919D)

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosion.

In the UK, the long-term (8-hour TWA) occupational exposure limits for starch are 10 mg/m^3 for total inhalable dust and 4 mg/m^3 for respirable dust.[27]

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Guide (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Amylopectin; α-amylose; maltodextrin; starch, pregelatinized; starch, sterilizable maize.

Amylopectin

CAS number: [9037-22-3]
Comments: amylopectin is a branched D-glucan with mostly α-D-(1→4) and approximately 4% α-D-(1→6) linkages.
The EINECS number for amylopectin is 232-911-6.

α-Amylose

CAS number: [9005-82-7]
Comments: amylose is a linear (1→4)-α-D-glucan.

18 Comments

Note that corn starch is also known as maize starch and that tapioca starch is also known as cassava starch.

Whereas the USPNF 23 specifies that starch should be produced from corn, potato, tapioca, or wheat, the BP 2004 also permits starch to be produced from rice. In tropical and subtropical countries where these starches may not be readily available, the BP 2004 additionally permits the use of tapioca starch, subject to additional requirements.

Starches from different plant sources differ in their amylose/amylopectin ratio. For example, corn starch contains about 27% amylose, potato starch about 22%, and tapioca starch about 17%. In contrast, waxy corn starch contains almost entirely amylopectin, with no amylose. These differences modify the physical properties of the starches such that the various types may not be interchangeable in a given pharmaceutical application. For example, amylose-rich maize starch has been studied as a potential tablet film-coating ingredient.[28]

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20 General References

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21 Authors

LY Galichet.

22 Date of Revision

25 August 2005.

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EXHIBIT 17

CLAIMS

1. A pharmaceutical composition containing micronized fenofibrate, a surfactant and a binding cellulose derivative as a solubilization adjuvant, characterized in that it contains an amount of fenofibrate greater than or equal to 60% by weight.

2. The composition as claimed in claim 1, characterized in that the binding cellulose derivative, which is a solubilization adjuvant, is hydroxypropylmethylcellulose.

3. The composition as claimed in claim 2, characterized in that the hydroxypropylmethyl-cellulose has an apparent viscosity of between 2.4 and 18 cP, preferably of between 2.4 and 3.6 cP.

4. The composition as claimed in one of claims 1 to 3, characterized in that it contains an amount of fenofibrate, greater than or equal to 70% by weight, even more preferably greater than or equal to 75% by weight, relative to the weight of the composition.

5. The composition as claimed in one of the preceding claims, characterized in that the surfactant is chosen from the group made up of polysorbate® 80, Montane® 20 and sodium lauryl sulfate.

6. The composition as claimed in one of the preceding claims, characterized in that the surfactant represents between 1 and 10%, preferably between 3 and 5%, by weight relative to the weight of the fenofibrate.

7. The composition as claimed in one of claims 2 to 6, characterized in that the fenofibrate/HPMC mass ratio is between 5/1 and 15/1.

8. The composition as claimed in one of the preceding claims, characterized in that the binding cellulose derivative represents between 2 and 15%, preferably between 5 and 12%, by weight of the composition.

9. The composition as claimed in one of the preceding claims, characterized in that it contains at least one excipient such as a diluent, for instance lactose, an antifoaming agent, for instance Dimethicone® or Simethicone®, or a lubricant, for instance talc.

10. The composition as claimed in one of the preceding claims, characterized in that the mean size of the fenofibrate particles is less than 15 µm, preferably less than 8 µm.

11. The composition as claimed in one of the preceding claims, characterized in that it is in the form of gelatin capsules containing powder or granules.

12. A method for preparing the composition as claimed in one of the preceding claims, characterized in that granules are prepared by assembly on neutral microgranules, by spraying an aqueous suspension containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension.

13. The method for preparing the composition as claimed in one of claims 1 to 11, characterized in that granules are obtained by wet granulation of powder, according to which the constituents, including in

constituents, including in particular the micronized fenofibrate, the surfactant and the cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried and calibrated.

EXHIBIT 18

REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

Status

As is correctly reflected in the Office Action Summary, Claims 1-13 are pending. Claims 1-13 stand rejected. Acknowledgement has been made to a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f) and copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau.

Summary of Amendments

By the foregoing amendments, the Specification has been amended to include an Abstract, as requested by the Examiner.

Also by the foregoing amendments, Applicants have amended Claims 1-13 to remove multiple dependencies; to correct minor and/or grammatical inconsistencies; and to remove "preferably . . . " language. The correction of the typographical error in Claim 13 is supported by, *inter alia*, Page 3, Lines 31 to 36 of the Specification. New Claims 14-20 result from such amendments and, therefore, derive support from at least Claims 1-13 prior to amendment. Accordingly, no new matter has been added.

Also by the foregoing amendments, Applicants have amended Claims 5 and 9 (and added claim 19) to delete the formerly-recited trade names and to add the

corresponding chemical description, as requested by the Examiner. No new matter has been added.

Rejection Under 35 U.S.C. § 112, Second Paragraph – Indefiniteness

Claims 3-6 and 8-10 were rejected under 35 U.S.C. § 112, Second Paragraph, as purportedly indefinite. *See Office Action mailed January 12, 2004, Pages 2-4*. This rejection is respectfully traversed.

Not to acquiesce in the Examiner's rejection, but solely to facilitate prosecution, Applicants have amended Claims 1-13 to delete material rejected by the Examiner, including ranges, the phrase "for instance," and trade names. New Claims 14-20 are free of such material.

From the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, Second Paragraph, indefiniteness rejection of Claims 1-13.

Minor Claim Informalities

Claims 5-12 were noted as reciting the expression "claimed in one of the preceding claims." *See Office Action mailed January 12, 2004, Page 4*. By the foregoing amendments, this expression has been deleted from the Claims. Accordingly, Applicants believe this informality issue has been rendered moot.

Rejection Under 35 U.S.C. § 103(a) – Stamm and/or DeBoeck

Claims 1-13 were rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over U.S. Patent No. 6,074,670 to Stamm *et al.* ("Stamm") or U.S.

Patent No. 5,545,628 to Deboeck *et al.* ("Deboeck") in view of Stamm. *See Office Action mailed January 12, 2004, Pages 4-6.* This rejection is respectfully traversed.

When applying 35 U.S.C. § 103, four tenets of patent law must be adhered to: (1) the claimed invention must be considered as a whole, (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination, (3) the references must be viewed without the benefit of impermissible hindsight vision, and (4) a reasonable expectation of success is the standard with which obviousness is determined. *See MPEP § 2141*, citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 (Fed. Cir. 1986). To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See MPEP § 2142.*

Moreover, mere identification of each claimed element in the prior art is not sufficient to negate patentability. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Instead, there "must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the filed of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 536 (Fed. Cir. 1998). Otherwise, sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. *Rouffet*, 149 F.3d at 1357.

Applicants maintain that a *prima facie* case of obviousness has not been made out and that the Examiner has merely identified elements of Applicants' invention in the cited publications.

Stamm

Applicants respectfully assert that Stamm does not contain or suggest all of the claimed limitations.

Stamm pertains to a pharmaceutical composition containing micronized fenofibrate, a surfactant, and a hydrophilic polymer having increased solubility, thereby allowing increase bioavailability. *See Stamm, Abstract*. Stamm specifies that in such compositions, the fenofibrate represents from 5 to 50% by weight, and preferably from 20 to 45% by weight, relative to the weight of the composition. *See, e.g., Stamm Column 4, Line 66 to Column 5, Line 7*.

Contrarily, the compositions of Claims 1-20 require fenofibrate contents greater than or equal to 60% by weight, relative to the weight of the composition. Therefore, Stamm does not teach all limitations of Claims 1-20 and may not be used on its own to establish a *prima facie* case of obviousness.

Turning now to the second criteria for establishing prima facie obviousness, one would not expect to arrive at Applicants' easily-administered fenofibrate compositions based on the content of Stamm. Specifically, Stamm indicates that the hydrophilic polymer (any substance with a high molecular weight) has an affinity for water sufficient to allow dissolution and formation of a gel, such as polyvinylpyrrolidone (PVP), poly(vinyl alcohol), hydroxypropylcellulose,

hydroxymethylcellulose, hydroxypropylmethyl-cellulose (HPMC), gelatin, etc.; the preferred hydrophilic polymer being PVP. *See Stamm, Column 4, Lines 14-26.* Example 1 of Stamm prepares granules containing 31.6% PVP and 31.6% micronized fenofibrate (100 ÷ (100 + 100 + 114.3 + 2.0)) that results in tablets containing but 17.7% micronized fenofibrate (100 ÷ (100 + 100 + 114.3 + 2.0 + 92.7 + 145.7 + 5.8 + 3.3)). *See Stamm, Column 7, Lines 40-50.* Therefore, two tablets according to Example 1 of Stamm would be required to deliver 200 mg of fenofibrate (such as in Lipanthyl® 200M).

Applicants' invention, comprising greater than or equal to 60% micronized fenofibrate (recall, Stamm establishes a fenofibrate maximum of 50%), a surfactant , and a binding cellulose derivative, overcomes the inefficiency of Stamm by involving a low proportion of binder and, therefore, a formulation of a smaller size. *See, e.g., Specification Page 3, Lines 9-16.* Moreover, Applicants' invention even provides bioavailability at least equal to that of Lipanthyl® 200M. *See Examples 1-2.* Prior to Applicants' invention, one reading Stamm would not have expected to succeed in arriving at such a composition, especially in light of the 50% fenofibrate maximum established by Stamm.

In light of the foregoing, Applicants assert that a *prima facie* case of obviousness over Stamm has not been established.

Deboeck

Applicants respectfully assert that there is no suggestion or motivation to both combine and modify the teachings of Stamm and Deboeck.

First, unlike Stamm, Deboeck permits a range of fenofibrate from 5 to 95%, and prefers a range from 45 to 55%. *Deboeck, Column 3, Lines 49-62*. Second, unlike both Applicants' and Stamm's compositions, the compositions of Deboeck do not contain *micronized* fenofibrate. Third, Deboeck indicates a molten solution of non-micronized fenofibrate-polyglycolized glycerides which is subsequently allowed to cool. Deboeck adds a cellulose derivative into the molten suspension as a stabilizer which avoids the formation of fenofibrate crystals during cooling. *See Deboeck, Column 2, Lines 43-54*. Stamm, however, incorporates micronized fenofibrate into an aqueous or organic solvent.

Given the contrasting natures of Stamm and Deboeck with respect to at least these three components, Applicants maintain that one would not have been motivated to combine these two publications.

Regarding modification of Stamm and Deboeck, Applicants maintain that not only do these publications fail to motivate one to arrive at Applicants' invention, they actually teach away from doing so. As described above, Stamm sets forth a limit of 50% micronized fenofibrate and Deboeck prefers no more than 55%, whereas Applicants use at least 60%.

With respect to the cellulose derivative, contrary to Stamm and Deboeck, Applicants' invention uses the cellulose derivative, such as HPMC, as a solubilization adjuvant (as set forth in Claim 1). While preparing Applicants' formulation, this polymer is intimately mixed with the fenofibrate microparticles, allowed by the solubilization of the polymer in the suspension which contains the microparticles of fenofibrate and the surfactant. It is performed by the recrystallization of the

molecules of the polymer onto the surface of the particle of the active principle during drying, forming a layer of hydrophilic molecules onto the surface of the insoluble particles of the active principle, thereby making them soluble (or more soluble), and increasing the bioavailability of fenofibrate. Therefore, increase in contact between the active principle and polymer results in increase of bioavailability. Prior to Applicants' invention, one would have promoted such contact by simply increasing the proportion of polymer relative to fenofibrate, seeking to reach saturation.

From the foregoing, Applicants maintain that a *prima facie* case of obviousness has not bee made out. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection of Claims 1-13 over Stamm or Stamm in view of Deboeck.

CONCLUSION

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 838-6526 so that prosecution of the application may be expedited.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: May 5, 2004

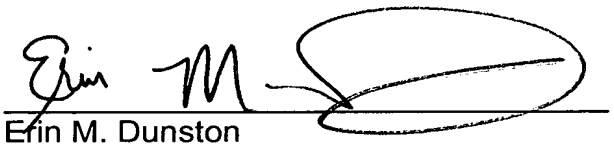
By: 
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EXHIBIT 19

REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.114, are respectfully requested.

Status

Claims 1-20 are pending, and all stand rejected. *See Office Action mailed September 22, 2004, pp. 2-3.*[1] Applicants' Amendment and Reply of May 5, 2004, eliminated the 35 U.S.C. § 112, First Paragraph indefiniteness rejections and the minor claim informalities.

Summary of Amendments

Applicants amend the specification at page 5, lines 31-34 to correct a translation error. In the original application, the French expression "suspension aqueuse" was erroneously translated as "aqueous solution." The correct translation of "suspension aqueuse" is "aqueous suspension" as now appears in the amended paragraph.

Applicants amend Claim 1 to specify that "said binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of the composition." The Specification supports the amendment at, e.g., p. 4, Lines 30-33. No new matter has been added.

Applicants cancel Claim 8 without prejudice or disclaimer.

[1] The Final Office Action Summary incorrectly states that Claims 14-20 are pending.

Applicants amend Claim 11 to read "wherein said composition is in the form of powder or granules, optionally contained in gelatin capsules." The Specification supports the amendment, e.g., original Claim 11. No new matter has been added.

Applicants add new Claims 21-46. The Specification supports those claims at, e.g., p. 3, Line 18 - p. 4, Line 24, and p. 5, lines 31-34. Specifically, Applicants have added claims reciting the ratio of fenofibrate/cellulose derivative (21); and claiming the suspension resulting from claim 11 (38). No new matter has been added.

Rejection Under 35 U.S.C. § 103(a) – Stamm and/or DeBoeck

Claims 1-20 were rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over U.S. Patent No. 6,074,670 to Stamm *et al.* ("Stamm") or U.S. Patent No. 5,545,628 to Deboeck *et al.* ("Deboeck") in view of Stamm. *Office Action, September 22, 2004, pp. 2-6.* Applicants traverse the rejection.

Neither of the cited references suggests the present invention, nor does the combination. Neither reference teaches or suggests the fabrication of a pharmaceutical composition comprising micronized fenofibrate present in an amount greater than 60% by weight of the composition, and a binding cellulose derivative of 2 to 15% by weight of the composition.

Stamm

Stamm teaches away from the present invention. Stamm states that a pharmaceutical composition of micronized fenofibrate can be formulated into a tablet wherein 20 to 50% by weight of the composition is fenofibrate (Stamm, col. 5, lines 1-7); and wherein the hydropyhilic polymer solubilizing agent is at least 20% by

weight of the composition (Stamm, col. 3, lines 11-23, "said hydrophilic polymer making up at least 20% by weight of (a)...." emphasis added).

The Examiner has taken the position that the claimed invention is mere optimization of the composition taught by Stamm. Applicants disagree. The claimed invention is outside the ranges taught by Stamm, and runs contrary to the teaching of Stamm. Thus, the claimed invention is not obvious over Stamm, or Stamm with DeBoeck.

"Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." MPEP §2144.05.II.A, *Optimization Within Prior Art Conditions Or Through Routine Experimentation* (emphasis added). Here, however, the cited art does not encompass the claimed invention, nor do the ranges of the art abut the claimed ranges. Rather, both the claimed ranges are substantially outside those of the reference.

Stamm unequivocally states that the hydrophilic polymer must be at least 20% by weight. (Stamm, col. 3, lines 11-23). Thus, the reference teaches that the hydrophilic polymer can not be below 20% by weight.

The reference also states that the fenofibrate represents up to 50% by weight of the composition. The reference does not explicitly state that the composition can not contain greater than 50% by weight fenofibrate, but neither does it suggest that compositions can be formulated having greater than 50% fenofibrate.

Stamm neither encompasses nor abuts the claimed invention, and thus the claimed invention is not merely optimization within prior art conditions or through routine experimentation.

Furthermore, the deviation from the cited reference is not optimization of a result-effective variable because the modification runs contrary to the desired result. "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP §2144.05.II.B. While it might be argued that applicants modified a result-effective variable, it was modified in a way that would have been expected to produce an effect opposite that intended, i.e., diminished dissolution. The result is unexpected, and thus nonobvious.

Fenofibrate is insoluble in water, and thus has poor dissolution and bioavailability on oral administration. Stamm purportedly overcomes that deficiency by, among other things, formulating a composition of micronized fenofibrate in a hydrosoluble carrier. The hydrosoluble carrier includes a hydrophilic polymer, which enhances dissolution of the fenofribrate. To achieve the desired dissolution profile, Stamm states that the hydrophilic polymer must be at least 20% of the composition, suggesting that greater quantities would produce a better dissolution profile.

In contrast, applicants modified the variable in the opposite direction, decreasing the hydrophilic polymer while improving the dissolution profile. Going contrary to the art is the antithesis of obviousness.

Stamm emphasizes that the fenofibrate composition includes, as a significant essential component, the hydrophilic polymer and that improved dissolution of the composition is allowed provided that the hydrophilic polymer represents at least 20% by weight of element (a); and preferably 25-45% by weight, or more than 25% by weight of element (a). Stamm, col. 5, lines 4-12. Stamm further states "the weight

ratio fenofibrate/hydrophilic polymer can, for example, be comprised between 1/10 and 4/1, preferably, for example, between 1/2 and 2/1." According to Stamm's teaching, the fenofibrate represent from 5 to 50% by weight, preferably, from 20-45% by weight of element (a). Col. 4, line 66 - col. 5, line 7.

Further, the ratio fenofibrate/binding cellulose derivative of the claimed composition is between 5/1 and 15/1; while the ratio fenofibrate/hydrophilic polymer of Stamm is between 1/10 and 4/1.

Applicants' invention provides a fenofibrate composition having greater dissolution and bioavailability in a composition comprising greater than or equal to 60% micronized fenofibrate, a surfactant , and a binding cellulose derivative. The composition overcomes deficiencies of Stamm's compositions by using less binder and producing a formulation of equivalent dosage but smaller size. *See, e.g., Specification p. 3, lines 9-16; and p. 3, line 37 – p. 4, line 4.*

Prior to Applicants' invention, one would not have expected such properties, especially in light of Stamm's teaching that fenofibrate must be 50% (wt) or less, and the hydrophilic polymer must be at least 20% (wt). Applicants went squarely against Stamm by increasing fenofibrate above 50% (wt), and decreasing hydrophilic polymer below 20%. This is the antithesis of obviousness. Applicants respectfully request reconsideration and withdrawal of the rejection.

Deboeck

There is no suggestion or motivation to both combine and modify the teachings of Stamm and Deboeck to arrive at the present invention.

There are important differences between DeBoeck and Stamm. First, Deboeck permits a range of fenofibrate from 5 to 95%, but prefers a range from 45 to 55%. *Deboeck, col. 3, lines 49-62.*

Second, unlike both Applicants' and Stamm's compositions, Deboeck's compositions do not contain *micronized* fenofibrate.

Third, Deboeck teaches use of a molten solution of *non-micronized fenofibrate-polyglycolized glycerides*, which is subsequently cooled. Deboeck adds a cellulose derivative into the molten suspension as a stabilizer, which allegedly avoids the formation of fenofibrate crystals during cooling. *Deboeck, col. 2, lines 43-54.* Stamm, however, teaches the use of micronized fenofibrate, and that it must be formulated in an aqueous or organic solvent.

In DeBoeck, HPMC is cited as a suspension stabilizer to the molten solution of fenofibrate-polyglycolized glycerides. DeBoeck states: "the suspension stabilizer avoids the formation of fenofibrate crystals during cooling of the filled hard gelatin capsules." DeBoeck, col. 2, lines 44-55. DeBoeck teach the use of HPMC only when the fenofibrate composition contains polyglycolized glycerides. If the fenofibrate composition does not contain polyglycolized glycerides, there is no need of a suspension stabilizer such as HPMC.

Given the contrasting natures of Stamm and Deboeck with respect to the various components, one would not have been motivated to combine those two references. Even if one were so motivated, there has been no showing that such a combination would have been as claimed, or that it would have produced a pharmaceutical composition having the intended properties.

The rejection asserts that the combination of references is proper as the claims are directed to a composition and not the process of preparing the composition. However, the selection of materials is highly relevant to the properties of the resulting composition, and goes directly to the issue of motivation to combine. Further, the two references describe compositions containing substantially different constituents in substantially different quantities, and there is no showing of any motivation for selecting the teaching of one over the other in those aspects where the two references diverge. Nor is there any showing that such a motivating teaching, if there is one, would produce the claimed invention. Without some motivation to combine the references, and to resolve the differences between the two in a manner that would produce the claimed invention, there is no *prima facie* showing of obviousness. Accordingly, the rejection is improper and should be withdrawn.

From the foregoing, Applicants assert that the rejection does not establish a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the § 103(a) rejection of Claims 1-13 over Stamm, either alone or in combination with Deboeck.

CONCLUSION

The foregoing amendments and remarks overcome all outstanding rejections. Applicants respectfully request formal notification of allowance of all pending claims. If, however, the Examiner has any questions relating to this Amendment and Reply, or the application in general, applicants encourage the Examiner to contact their attorney by telephone at (703) 838-6526 to expedite examination and disposition of the case.

Respectfully submitted,
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EXHIBIT 20

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

LISTING OF CLAIMS:

1. (Previously presented) A pharmaceutical composition comprising micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization adjuvant, wherein said fenofibrate is present in an amount greater than or equal to 60% by weight, relative to the weight of the composition, and further wherein said binding cellulose derivative represents between 2 to 15% by weight, relative to the weight of the composition.

2. (Previously Presented) The composition of claim 1, wherein said binding cellulose derivative is hydroxypropylmethylcellulose.

3. (Previously Presented) The composition of claim 2, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 18 cP.

4. (Previously Presented) The composition of claim 1, wherein said fenofibrate is present in an amount greater than or equal to 70% by weight, relative to the weight of the composition.

5. (Previously Presented) The composition of claim 1, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

6. (Previously Presented) The composition of claim 1, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of the fenofibrate.

7. (Previously Presented) The composition of claim 2, wherein said fenofibrate/HPMC mass ratio is between 5/1 and 15/1.

8. Cancelled.

9. (Previously Presented) The composition of claim 1, wherein said composition further comprises at least one excipient.

10. (Previously Presented) The composition of claim 1, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

11. (Previously presented) The composition of claim 1, wherein said composition is in the form of powder or granules, optionally contained in gelatin capsules.

12. (Previously Presented) A method for preparing the composition of claim 11, wherein said granules are prepared by assembly on neutral microgranules, by spraying an aqueous suspension containing the surfactant, the solubilized binding cellulose derivative and the micronized fenofibrate in suspension.

13. (Previously presented) The method for preparing the composition of claim 11, wherein said granules are obtained by wet granulation of powder, according to which the constituents, including in particular the micronized fenofibrate, the surfactant and the binding cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried and calibrated.

14. (Previously Presented) The composition of claim 3, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 3.6 cP.

15. (Previously Presented) The composition of claim 1, wherein said fenofibrate is present in an amount greater than or equal to 75% by weight, relative to the weight of the composition.

16. (Previously Presented) The composition of claim 1, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of the fenofibrate.

17. (Previously Presented) The composition of claim 1, wherein said binding cellulose derivative represents between 5 and 12% by weight, relative to the weight of the composition.

18. (Previously Presented) The composition of claim 9, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

19. (Previously Presented) The composition of claim 9, wherein said excipient is selected from the group consisting of lactose, α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)], a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide, and talc.

20. (Previously Presented) The composition of claim 1, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

21. (Previously presented) A pharmaceutical composition comprising micronized fenofibrate, a surfactant, and a binding cellulose derivative as a solubilization agent, wherein the mass ratio of fenofibrate to binding cellulose derivative is between 5/1 and 15/1.

22. (Previously presented) The pharmaceutical composition according to claim 21, wherein the binding cellulose derivative is hydroxypropylmethylcellulose.

23. (Previously presented) The composition of claim 21, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 18 cP.

24. (Previously presented) The composition of claim 21, wherein said binding cellulose derivative has an apparent viscosity of between 2.4 and 3.6 cP.

25. (Previously presented) The composition of claim 21, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

26. (Previously presented) The composition of claim 21, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of fenofibrate.

27. (Previously presented) The composition of claim 21, wherein said surfactant represents between 3 and 5% by weight, relative to the weight of fenofibrate.

28. (Previously presented) The composition of claim 21, wherein said composition further comprises at least one excipient.

29. (Previously presented) The composition of claim 28, wherein said excipient is selected from the group consisting of a diluent, an antifoaming agent, a lubricant, and a mixture thereof.

30. (Previously presented) The composition of claim 29, wherein said diluent is lactose.

31. (Previously presented) The composition of claim 29, wherein said antifoaming agent is α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] or a mixture of α-(trimethylsilyl)-ω-methylpoly[oxy-(dimethylsilylene)] with silicon dioxide.

32. (Previously presented) The composition of claim 29, wherein said lubricant is talc.

33. (Previously presented) The composition of claim 21, wherein said micronized fenofibrate has a mean particle size less than 15 μm.

34. (Previously presented) The composition of claim 21, wherein said micronized fenofibrate has a mean particle size less than 8 μm.

35. (Previously presented) The composition of claim 21, wherein said composition is in the form of granules or powder, optionally contained in gelatin capsules.

36. (Previously presented) A method for preparing the composition of claim 35, wherein said granules are prepared by assembly on neutral microgranules, by spraying an aqueous suspension containing the surfactant, solubilized binding cellulose derivative, and the micronized fenofibrate in suspension.

37. (Previously presented) A method for preparing the composition of claim 35, wherein said granules are obtained by wet granulation of powder, wherein the

constituents, including the micronized fenofibrate, the surfactant, and binding cellulose derivative, are granulated by wet granulation using an aqueous wetting solution, dried, and calibrated.

38. (Previously presented) An aqueous suspension containing micronized fenofibrate in suspension, a solubilized binding cellulose derivative, and a surfactant, wherein the mass ratio of said fenofibrate to binding cellulose derivative is between 5/1 and 15/1.

39. (Previously presented) The suspension according to claim 38, wherein said binding cellulose derivative is hydroxypropylmethylcellulose.

40. (Previously presented) The suspension according to claim 39, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 18 cP.

41. (Previously presented) The suspension according to claim 39, wherein said hydroxypropylmethylcellulose has an apparent viscosity of between 2.4 and 3.6 cP.

42. (Previously presented) The suspension according to claim 38, wherein said surfactant is selected from the group consisting of polyoxyethylene 20 sorbitan monooleate, sorbitan monododecanoate, and sodium lauryl sulfate.

43. (Previously presented) The suspension according to claim 38, wherein said surfactant represents between 1 and 10% by weight, relative to the weight of fenofibrate.

44. (Previously presented) The suspension according to claim 38, wherein said micronized fenofibrate has a mean particle size less than 15 µm.

45. (Previously presented) The suspension according to claim 38, wherein said micronized fenofibrate has a mean particle size less than 8 µm.

46. (Previously presented) A method of preparing granules of fenofibrate, comprising the step of spraying the suspension according to claim 38 onto neutral microgranules.

47. (New) The composition of claim 2 achieving 95% dissolution in vitro at 30 minutes.